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EXAMINER

BAKER, MAURIE GARCIA

ART UNIT PAPER NUMBER

1639

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/456,429

Applicant(s)

JI et al

Examiner

Maurie G. Baker, Ph.D.

Art Unit

1639



-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 22, 2002

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1035 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 74-83 is/are pending in the application

4a) Of the above, claim(s) 75-77 and 79 is/are withdrawn from consideration

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 74, 78, and 80-83 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

4) ☐ Interview Summary (PTO-413) Paper No(s). _____

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) ☐ Notice of Informal Patent Application (PTO-152)

3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) ☐ Other: _____

DETAILED ACTION

Please note: The number of Art Unit 1627 has been changed to 1639. Please direct all correspondence for this case to Art Unit 1639.

1. The Response filed October 22, 2002 (Paper No. 21) is acknowledged. Claim 81 was amended and no claims were cancelled or added. Therefore, claims 74-83 are pending.

2. Claims 75-77 and 79 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, there being no allowable generic claim.

3. Thus, claims 74, 78 and 80-83 are currently under examination.

Status of Rejections

4. The previous rejection under the second paragraph of 35 U.S.C. 112 is withdrawn in view of applicant's claim amendment. The rejection under 35 U.S.C. 103(a) over Pifferi et al is withdrawn in view of applicant's arguments, which were found persuasive. However, a *new* rejection based on these arguments is set forth below (see paragraphs 9-10). Since this rejection was not necessitated by an amendment to the claims, the case remains in non-final status. A new claim objection (to claim 83) is also set forth.

5. Also, the terminal disclaimer filed on October 22, 2002 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,420,560 has been reviewed and is accepted. The terminal disclaimer has been recorded.

6. Lastly, new art rejections based on a non-elected species are also set forth in this action. With respect to the species election, see MPEP § 803.02 (emphasis added):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. *The prior art search, however, will not be extended unnecessarily to cover all nonelected species.* Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Claim Objections

7. Claim 83 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). It is suggested for the claim to read "...compound of **any of** claims 74-82" (emphasis added).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 74, 78 and 80-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds with L moieties of formulas (i), (ii), (iii) and (v), does not reasonably provide enablement for compounds with L moieties of formulas (iv) and (vi). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with L moieties of formulas (i), (ii), (iii) and (v); however, there is insufficient guidance as to how to make and *use* compounds with L moieties of formulas (iv) and (vi). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims and the nature of the invention: The claims are drawn to compounds of formula $L - X - L$ where the L moieties can be of seven structurally different formulas and X is a linker linking the moieties. This represents broad scope. The nature of the invention is pharmaceutical use of compounds of formula $L - X - L$ as calcium channel drugs.

The state of the prior art and the level of predictability in the art: The state of the art (organic & medicinal chemistry) at the time of filing was such that the *use* of compounds with L moieties of formulas (iv) and (vi) would not be predictable. To satisfy the enablement requirement, applicant must teach how to make *and* use the full scope of the claimed invention.

In the Response filed October 22, 2002, applicant argues against the obviousness of various attachment sites in dimeric compounds in response to the examiner's previous rejection of the claims under 35 U.S.C. 103 over Pifferi et al (US 5,120,730; of record). This reference teaches dimeric benzothiazepines, see Abstract and patented claims. The benzothiazepines made by Pifferi et al have "structures related to diltiazem", which is a known calcium antagonist (see column 1, lines 6-28, especially lines 11-14 & 21-24). This is also applicant's elected species of ligand. The compounds of the Pifferi reference read on those of the claims when the ligands are of formula (iv) or (vi). The dimeric benzothiazepines of Pifferi et al are linked by a linker moiety denoted X, which can be, for example, $-CH=CH-$, $-(CH_2)_2-$ or $p-C_6H_4$ (see patented claim 2). The linker of Pifferi reads on the claimed linker. Pifferi et al differs from the instant

claims only in the *linkage site* for the two benzothiazepine ligands. Applicant argues that one of ordinary skill would not be motivated to vary the linkage sites of a dimeric benzothiazepine from those of Pifferi et al to those of the claims in view of the teachings of Inoue et al (J. Med. Chem., 34(2):675-687 (1991); see paragraph 10 below) and Nagao et al (Chem. Pharm. Bull., 21(1):92-97 (1973); see paragraph 10 below). This is because the cited Inoue et al and Nagao et al references teach that substitution at sites other than those of Pifferi causes a decrease in potency. Specifically, these two references teach that bulky substituents on biologically active benzothiazepines at either of applicants claimed linkage sites (i.e. ligands of formula (iv) or (vi)) results in significant decreases in potency. See applicant's Response, page 6, and the below teachings of the references.

For example, for substitution at the dimethylamino site, i.e. formula (iv), see the following: Inoue et al: page 680 1st column, 2nd paragraph; and Nagao et al: Table III page 94. For example, for substitution at the 4-methoxyphenyl site, i.e. formula (vi), see the following: Inoue et al: page 680 1st column, 3rd paragraph; and Nagao et al: Table II page 94. These teachings for the two references show that bulky substituents at the dimethylamino and 4-methoxyphenyl sites of benzothiazepines are not well tolerated. Since the instant claims are drawn to addition of another entire ligand at these sites (*much* larger than any of the substituents of Inoue et al or Nagao et al) it would not be predictable that the claimed compounds would have any biological activity.

The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided *any* data on the activity of the claimed compounds with L moieties of formulas (iv) and (vi). In fact, there is no activity data provided in the instant specification for any of the compounds. Thus, based on the teachings of Inoue et al and Nagao et al with respect to the lack of tolerance for bulky substituents for benzothiazepines at the linkage positions of the claimed ligands, it would not be predictable that the claimed compounds would have any activity whatsoever. In the Response filed October 22, 2002 (page 6, bottom through page 7), applicant states that “attaching the linker to a different site on the moiety would cause conformational changes in the resulting molecule with unknown affects on the compound’s biological activity” and that the Inoue et al and Nagao et al references teach away from such linkages (the examiner has elaborated on this point above). Applicant also states that “*one skilled in the art would not have a reasonable expectation that Applicants’ presently claimed compounds would have calcium channel antagonistic activity*” (page 7, 1st full paragraph, emphasis added). Moreover, applicant states that “*attaching the linker to a different site on the moiety would significantly affect the conformational structure of the compounds and the effect of such a*

*conformational change on a compound's biological activity is **highly unpredictable***" (page 7, 4th full paragraph, emphasis added).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in using the full scope of the claimed compounds due to the deficiencies described above. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

10. Please also note that because applicant has provided copies of the references to the examiner (as an attachment to the Response filed October 22, 2002 (Paper No. 21)), a copy of these references is not included with this action. However, the references have been cited on a PTO-892 for completeness since they were not provided as a formal Information Disclosure Statement.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 74 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Menta et al (EP 0 266 549).

Menta et al disclose a compound that reads directly on those of the claims containing two ligands (L) of formula (v). Specifically see Example 6, page 13, particularly compound in lines 38-39. This compound has two ligands reading directly on formula (v) and the linker in the compound reads on the X of the claims when $m = 0$; 1st X' = bond; 1st Z = alkenylene; Y'' = bond; 2nd Z = substituted arylene; and 2nd X' = alkylene. The reference also discloses pharmaceutical compositions, see claim 9.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 74 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over either of Devlin et al (US 4,725,597) or EP 0 122 488.

Devlin et al disclose dimeric (bis) piperazinyl alkanes that read directly on the multibinding compounds of the instant claims (see Abstract). The ligands (L) are of formula (v), and the linker (X) is alkyl and the compounds are homomeric. Specifically, see compounds described in the Abstract, preferred compounds described in columns 4-5 and Example 8 of the patent. The reference also discloses pharmaceutical compositions, see patented claims 19 and 20 and Examples 37-39.

EP 0 122 488 (also having Devlin as an inventor) appears to have the same or similar teachings as the above US patent. The reference is in German, however, the teachings thereof are evident from the structures disclosed (see

Abstract and claim 2, for example). Thus the compounds of this reference also read on the claimed multibinding compounds when the ligands (L) are of formula (v), and X is an alkyl linker. The reference also discloses pharmaceutical compositions, see pages 40-43. See attached printout from STN included for applicant's convenience.

In the alternative, if one interprets the above references as not specifically teaching the claimed fluoro substituents, the use of such would be obvious for the following reasons.

The references clearly teach compounds with halogen substitution (i.e. halogen in general and specifically chloro) and the use of any halogen at these positions would be deemed to be *prima facie* obvious due to their art recognized equivalence. See MPEP 2144.06. Also see MPEP 2144.09 with respect to close structural similarity between chemical compounds.

Status of Claims/Conclusion

16. No claims are allowed.
17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
January 9, 2003

A handwritten signature in black ink, appearing to be 'MB' followed by a long horizontal stroke.

MAURIE GARCIA BAKER, Ph.D.
PATENT EXAMINER